NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Mayhem in May: Susceptibility, Symptoms, Progression, and Complications of COVID-19

by

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Part I – Benign Beginnings

May 1, 2020

A 50-year-old male patient (50M) presented to his primary care physician with a three-day history of abdominal pain and mild pyrexia (99 °F). He reported a two-day history of nausea, watery diarrhea, and several episodes of emesis (vomiting). The patient also admitted to having hematemesis (vomiting of blood) and hematochezia (blood in stool). Physical examination revealed moderate abdominal tenderness, tachycardia, and mild dyspnea. A chest x-ray was ordered and did not display any evidence of abnormalities.

The patient's medical record reported a history of stomach ulcers but was otherwise unremarkable. The patient admitted to visiting his aunt in rural Wisconsin the previous week to celebrate her 80th birthday, where he consumed his favorite food, poached eggs. The patient revealed that his gastrointestinal symptoms started five days after his return.

A stool sample was collected to check for *Salmonella* infection. In the meantime, the physician advised increased fluid intake to prevent dehydration and administered prophylactic azithromycin to avoid complications as a result of the patient's history of stomach ulcers. No COVID test was performed during this visit.

May 4, 2020

50M's condition did not improve and he developed high-grade pyrexia (101 °F). After three additional days, he continued to complain of malaise and onset of dyspnea. His wife was concerned and remembered that they had a pulse oximeter at home. Her father-in-law's cardiologist had given the oximeter, along with instructions on how to use it, when he was hospitalized the previous year. She placed the pulse oximeter on her husband's index finger to check his oxygen saturation and was alarmed to see it consistently reading at 85%. She quickly called for an ambulance and he was rushed to the hospital. He was admitted to the emergency room and he provided his history to the medical team. His physician ordered a nasopharyngeal swab test and collected stool samples. These samples were tested using real time polymerase chain reaction (RT-PCR) to detect viral infection. His test results identified the presence of SARS-CoV-2 nucleic acid and absence of influenza virus types A and B.

May 6, 2020

50M's condition worsened as indicated by increased levels of inflammatory markers (Table 1) and presence of viral RNA in respiratory samples and feces. Bacterial and fungal cultures of blood and lower respiratory tract specimen turned out to be negative. Chest x-ray indicated fluid in the lungs, possibly due to pneumonia, and computed tomography (CT) scan revealed lesions that covered 30% of the lung surface**.** Comprehensive metabolic panel indicated severe inflammation, with elevated liver enzymes, inflammatory markers, lymphopenia (lower level of white blood cells), and alkalosis with normal kidney function (Tables 1 and 2). Since his oxygen saturation continued to drop to 81%, he was placed on standard oxygen at 5 L per minute, treated with acetaminophen to reduce fever, and given the antiviral medication remdesivir.

Table 1. Laboratory parameters for patient 50M on May 6, 2020.

*Component**	*Normal range (male)*	*Patient's value*
ALT (U/L)	10–40	146
LDH (U/L)	80–225	756
ALB (g/dL)	3.5–5.5	3.24
Lymphocytes ($U \times 10^3/\mu L$)	1.0–4.8	0.50
Neutrophils ($U \times 10^3/\mu L$)	1.8–7.7	9.4
Red blood cells ($U \times 10^6/\mu L$)	4.7–6.1	4.5
Hemoglobin (g/dL)	14–18	12.0
C-reactive protein (mg/L)	<5	150.6
Serum ferritin (ng/mL)	24–336	1965.3
ESR (mm/h)	<15	83
IL-6 (pg/mL)	0.1–2.9	25.2
D-dimer (µg/mL)	<=0.50	0.86
SAA (mg/L)	0–10	170.6
FIB (mg/dL)	200–400	581
BUN (mg/dL)	6–20	5.6
Creatinine, serum (mg/dL)	0.6–1.3	0.75

* *Abbreviation key:* ALB, albumin (a plasma protein); ALT, alanine aminotransferase (liver function test); BUN, blood urea nitrogen (kidney function test); ESR, erythrocyte sedimentation rate (inflammation marker); FIB, fibrinogen (clotting function test); LDH, lactic dehydrogenase (cell death marker); SAA, serum amyloid A (inflammation marker).

Table 2. Selected values from basic metabolic panel of Patient 50M on May 6, 2020.

Component	*Normal Range*	*Values*
pH	7.35–7.45	7.520
HCO_3^- (mmol/L)	22–26	26.8
PCO_2 (mmHg)	35–45	31.0
Glucose (mg/dL)	65–99	66

May 9, 2020

Both his breathing rate and heart rate were increased, and oxygen saturation was below 80%. 50M was moved to the intensive care unit (ICU) where he was placed on a non-invasive positive pressure ventilator (NPPV) with continued oxygen supplementation. An electrocardiogram (ECG) revealed nonspecific T wave abnormality in anterolateral leads along with sinus tachycardia.

Questions

1. What are the classic COVID-19 symptoms?
2. What are the less common symptoms reported by other COVID patients? Relate this to the symptoms exhibited by patient 50M and explain why the doctor did not perform a COVID test on May 1, 2020.
3. What are some of the commonly performed tests to confirm COVID-19 infection?
4. Identify the parameters for patient 50M (see Tables 1 and 2) that do not fall within the normal range. Which values are unexpected and why? Using the abbreviation key in Table 1, what are the systemic changes and which are the major organs affected by the infection?
5. What does the pulse oximeter measure? What is the normal reading in a healthy adult and what are the values presented by patient 50M?
6. Examine serum amyloid A and C-reactive protein levels in patient 50M. Why is serum amyloid A measured and explain how it differs from the information provided by measuring C-reactive protein?
7. Based on our current knowledge, how does SARS-CoV-2 infect human cells? Which are the commonly affected organs?
8. What are the different stages of SARS-CoV-2 infection? How does COVID-19 infection result in acute respiratory distress syndrome (ARDS)?
9. Of the abnormal values of patient 50M presented in Table 1, which are the ones that could be linked to the presentation of hematemesis and hematochezia? Speculate on how SARS-CoV-2 infects the digestive tract to induce hematemesis and hematochezia in patient 50M.
10. Based on the data provided and your analysis thus far, predict the potential outcomes for patient 50M.

Part II – Chaos Continues

A review of 50M's family history revealed that there are four additional people in his family, including his wife (45-year-old female, 45F), his daughter (13-year-old female,13F), his mother (80-year-old female, 80F), and his father (85-year-old male, 85M) (Figure 1).

13F was recently diagnosed with colitis and was taking a low-dose of prednisone, a steroidal medication, to reduce inflammation and diarrhea. 85M had a history of dyslipidemia, abnormal lipid profile, and previously had stents placed to correct coronary arteries blocked by atheroma, fatty plaque. 80F used eyedrops daily for glaucoma but had no additional remarkable medical history.

45F was worried about the increased susceptibility of 13F due to her steroid-induced immunosuppression and decided to prophylactically quarantine both herself and 13F to avoid the risk of infection, particularly involving the digestive tract. However, 80F and 85M were concerned about 50M's health, kept checking on him regularly despite 50M insisting that he would recover shortly with rest.

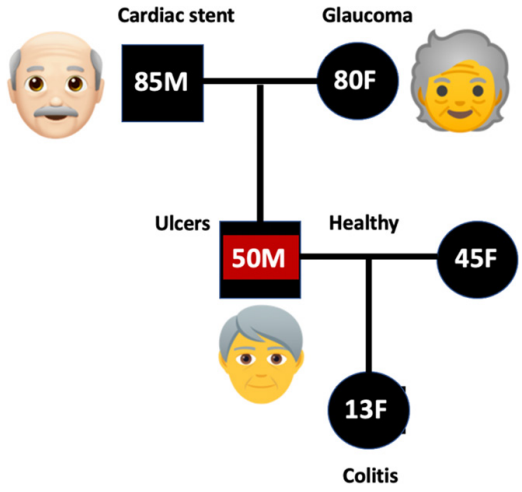

Figure 1. Pedigree tree and family history of patient 50M.

Once 50M tested positive for COVID-19, the hospital initiated contact tracing. The family and people 50M had interacted with over the past two weeks were immediately tested. Due to the timely quarantining efforts, both 45F and 13F tested negative for COVID-19.

80F and 85M both tested positive and were already reporting low-grade pyrexia. They were advised to quarantine, closely monitor their symptoms, and use pulse oximeters to continuously check oxygen saturation.

May 8, 2020

85M continued to experience cough, sore throat, and pyrexia (101°F), and developed dyspnea along with tachycardia. 80F also experienced shortness of breath and pyrexia, leading both to be admitted to the hospital.

85M's oxygen saturation dropped to 90% and, similar to 50M, biochemical tests indicated an inflammatory response (Table 3), accompanied with lymphopenia. A CT of the chest was ordered and ground-glass opacity was observed in both lungs (Figure 2B), more severe than that seen in 50M (Figure 2A). 85M was placed on supplemental oxygen at 5 L per minute and given remdesivir. This did not increase his oxygen saturation and in addition to tachycardia (abnor-

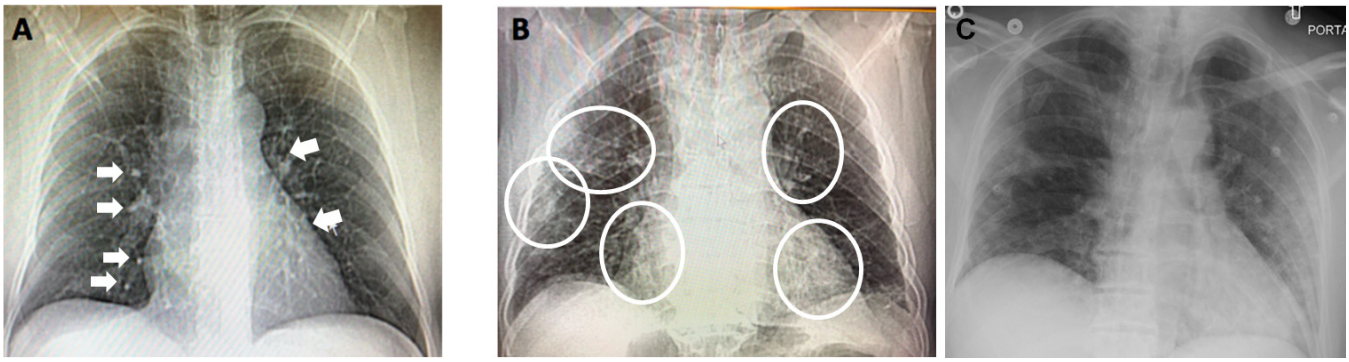

Figure 2. A, Chest CT scan of patient 50M (May 6, 2020) showed mild multifocal ground glass opacity (white arrows) seen in right and left upper lobes and posterior right lower lobe; Inference: most likely representing multifocal pneumonia. B, Chest CT scan of patient 85M (May 8, 2020) revealed heterogeneous ground glass density seen throughout the lungs (circled), with right greater than left. Inference: Moderate multifocal pneumonia with moderate to severe involvement of lower lobes. Findings consistent with known viral (COVID) pneumonia. C, Chest CT scan of patient 80F (May 8, 2020) showing no remarkable abnormalities. Inference: Normal, healthy lungs.

Table 3. Laboratory parameters comparing values for patients 85M and 50M.

*Component**	*Normal Range (Male)*	*Values for 85M (May 8, 2020)*	*Values for 50M (May 6, 2020)*
ALT (U/L)	10–40	84	146
LDH (U/L)	80–225	432.6	756
ALB (g/dL)	3.5–5.5	3.4	3.24
Lymphocytes (U×10^3/μL)	1.0–4.8	0.84	0.50
Neutrophils (U×10^3/μL)	1.8–7.7	7.0	9.4
Red blood cells (U×10^6/μL)	4.7–6.1	4.6	4.5
Hemoglobin (g/dL)	14–18	11.6	12.0
C-reactive protein (mg/L)	<5	120.5	150.6
Serum ferritin (ng/mL)	24–336	1094	1965.3
ESR (mm/h)	<15	82	83
IL-6 (pg/mL)	0.1–2.9	18.4	25.28
D-dimer (μg/mL)	<=0.50	0.74	0.86
SAA (mg/L)	0–10	125.2	170.6
FIB (mg/dL)	200–400	576	581
BUN (mg/dL)	6–20	7	5.6
Creatinine, serum (mg/dL)	0.6–1.3	0.85	0.75

* *Abbreviation key:* ALB, albumin (a plasma protein); ALT, alanine aminotransferase (liver function test); BUN, Blood urea nitrogen (kidney function test); ESR, erythrocyte sedimentation rate (inflammation marker); FIB, fibrinogen (clotting function test); LDH, lactic dehydrogenase (cell death marker); SAA, serum amyloid A (inflammation marker).

mally high heart rate), he developed tachypnea (fast breathing rate). He was moved to the ICU where they alternated the use of standard oxygen at 5 L per minute with that of high-flow nasal oxygen (HFNO) at 30 L per minute (fraction of inspired oxygen 100%) to increase oxygen saturation. After a few hours, his oxygen saturation decreased to 85%.

80F was experiencing low-grade pyrexia (99 °F) and mild dyspnea, but her symptoms were less severe than those experienced by 50M or 85M (Table 4). Her oxygen saturation was 94% and her chest x-ray and CT scan were unremarkable. 80F was placed on acetaminophen to reduce pyrexia and she continued to recover.

Table 4. Laboratory parameters for patient 80F on May 8, 2020.

*Component**	*Normal range (female)*	*Value*
ALT (U/L)	10–40	14.4
LDH (U/L)	80–225	152.6
ALB(g/dL)	3.5–5.5	4.0
Lymphocytes (U×10^3/μL)	1.0–4.8	1.39
Neutrophils (U×10^3/μL)	1.8–7.7	2.87
Red blood cells (U×10^6/μL)	4.2–5.4	4.21
Hemoglobin (g/dL)	12–16	12.8

C-reactive protein (mg/L)	<5	7.93
Serum ferritin (ng/mL)	11–307	113.5
ESR (mm/h)	<20	8
IL-6 (pg/mL)	0.1–2.9	4.27
D-dimer (μg/mL)	< 0.50	0.40
SAA (mg/L)	0–10	3.5
FIB (mg/dL)	200–400	371
BUN (mg/dL)	6–20	13
Creatinine, serum (mg/dL)	0.5–1.1	0.7

* Abbreviation key: ALB, albumin (a plasma protein); ALT, alanine aminotransferase (liver function test); BUN, Blood urea nitrogen (kidney function test); ESR, erythrocyte sedimentation rate (inflammation marker); FIB, fibrinogen (clotting function test); LDH, lactic dehydrogenase (cell death marker); SAA, serum amyloid A (inflammation marker).

May 12, 2020

80F's RT-PCR test indicated that she was negative for SARS-CoV-2. Meanwhile, 85M's oxygen saturation continued to drop from 65% in the prone position to 60% in the supine position.

May 14, 2020

Repeat test for SARS-CoV-2 came back negative for 80F and so after being hospitalized for six days, she was sent home with the anticoagulant, enoxaparin, to be taken once daily for the next few days. She was worried about the health condition of her husband and son, and reluctantly went home where she continued her quarantine.

Questions

11. Name the test that can be performed to determine if 50M's wife and daughter had past infections with the virus and if they are asymptomatic as a result.
12. Why did 45F believe that 13F had an increased susceptibility and risk of infection?
13. 85M's CT revealed ground-glass opacification in the lungs. What does this indicate?
14. Explain the importance of placing 50M in a prone position to help increase his oxygen saturation levels.
15. Comparing the severity of infection between the patients in this case, speculate on the reasons for such disparity in these individuals with COVID-19.
16. Looking at the data from the five members of this family, do you notice any interesting trends in sex-specific risk of contracting SARS-CoV-2 infection?
17. Why is 80F prescribed an anticoagulant before her discharge from the hospital?
18. Why is HFNO at 30 L per minute not to be used continuously to increase oxygen saturation?
19. Keeping in mind that 13F tested negative despite staying under the same roof as patients 50M, 85M and 80F, what do we currently know about the susceptibility of children to COVID-19?
20. Explain why severe forms of COVID-19 have occurred in elderly patients with cardiovascular comorbidities, such as seen in 85M.

Part III – Severe Loss

May 12, 2020

50M was in ICU for the past week. He was sedated, and his condition worsened. His oxygen saturation remained below 80% even in a prone position and dropped further to 72% when taken off the ventilator briefly every night. In addition to the ground glass opacity seen earlier, current imaging of the lungs showed increasing alveolar damage with mononuclear cells (specialized immune cells, including lymphocytes and monocytes), macrophages infiltrating air spaces, and a diffuse thickening of the alveolar wall. Differential blood count revealed marked lymphopenia with an increase in neutrophils (multilobed granulocytes). Blood and lower respiratory tract cultures were performed immediately, and this revealed the presence of a bacterial infection (*Staphylococcus aureus*) in the lungs, which was treated with the antibiotic cefazolin.

May 15, 2020

A repeat CT scan revealed the persistence of the diffuse thickening of the alveolar walls. Although 50M met all the eligibility requirements for convalescent plasma therapy, he was not in the initial stages of infection and the doctors were concerned about aggravating a hyperimmune attack. Interestingly, 50M's repeat viral RNA test for SARS-CoV-2 was negative, about 11 days after testing positive for COVID-19.

May 16, 2020

85M was admitted to the hospital on May 8, 2020 and his condition had since worsened. He could not be placed on a ventilator due to the pre-existing heart condition. Instead, he was administered high-flow nasal oxygen (HFNO) at 30 L per minute, which was alternated with standard oxygen at 5 L per minute. His oxygen saturation continued to drop, while his tachycardia and tachypnea worsened. His blood pH started to increase, he became disoriented, and at 6 PM, eleven days after symptoms first presented, 85M died from cardiac arrest.

May 18, 2020

The doctors continued treating 50M in prone position, administering oxygen at 30 L per min and maintaining him on helmet continuous positive airway pressure. However, his oxygen saturation did not increase above 67% and they continued to sedate him. There was a small gleam of hope as his test results showed a reduction in inflammatory markers. However, his liver enzymes kept increasing, warranting further investigation (Table 5, next page). Imaging (MRI) of the liver revealed a patch and subsequent PNA-FISH (peptide nucleic acid fluorescence *in situ* hybridization) assay for rapid identification of microbial organisms reported positive for *Candida albicans*. Fluconazole (8 mcg/ml per Kg body weight) was administered to treat this fungal infection. Doctors warned 45F that there could be adverse side effects as the fungal medication might also target human cells and cause organ damage.

May 22, 2020

50M continued to battle the virus after nearly four weeks of infection. He had been sedated for the past 14 days and his condition took a turn for the worse. The nurse noticed that his urine output had decreased. Biochemical analysis of blood revealed marked pH and electrolyte fluctuations with HCO_3^- (mmol/L) at 10.1 and a PCO_2 (mmHg) value of 27.9 (Table 6, next page). The ICU doctor informed the family that it would be a stormy night for 50M as they planned to perform dialysis in an attempt to restore pH and electrolyte balance. The doctors were concerned since this procedure required the patient to be moved from prone to supine position. They prepared him for the procedure at 10 PM and, while in the middle of the dialysis, his oxygen saturation bottomed out. 50M died at 11:30 PM due to COVID-induced multiorgan failure.

Table 5. Laboratory parameters for Patient 50M.

Components	*Normal range*	*Values May 18, 2020*	*Values May 6, 2020*
ALT (U/L)	10–40	279	146
LDH (U/L)	80–225	959	756
ALB (g/dL)	3.5–5.5	2.8	3.24
Lymphocytes ($U \times 10^3/\mu L$)	1.0–4.8	0.41	0.50
Neutrophils ($U \times 10^3/\mu L$)	1.8–7.7	14.3	9.4
Red blood cells ($U \times 10^6/\mu L$)	4.7–6.1	4.6	4.5
Hemoglobin (g/dL)	14–18	13.9	12.0
C-reactive protein (mg/L)	<5	219.6	150.6
Serum ferritin (ng/mL)	24–336	2250.7	1965.3
ESR (mm/h)	<15	95	83
IL-6 (pg/mL)	0.1–2.9	29.52	25.28
IL-1 (pg/mL)	0–5	26.78	-
TNF-alpha (pg/mL)	0–16	47.1	-
D-dimer (µg/mL)	<=0.50	1.06	0.86
SAA (mg/L)	0–10	215.3	170.6
BUN (mg/dL)	6–20	16	5.6
Creatinine, serum (mg/dL)	0.6–1.3	3.2	0.75
FIB (mg/dL)	200–400	727	581

* *Abbreviation key:* ALB, albumin (a plasma protein); ALT, alanine aminotransferase (liver function test); BUN, Blood urea nitrogen (kidney function test); ESR, erythrocyte sedimentation rate (inflammation marker); FIB, fibrinogen (clotting function test); LDH, lactic dehydrogenase (cell death marker); SAA, serum amyloid A (inflammation marker).

Table 6. Selected values from basic metabolic panel of Patient 50M on May 18, 2020.

Component	*Normal Range*	*Values*
pH	7.35–7.45	6.98
HCO_3^- (mmol/L)	22–26	10.1
PCO_2 (mmHg)	35-45	27.9
Glucose (mg/dL)	65–99	66

Questions

Use the table below, or create a similar table, to track the clinical history and course of the infection among the members of the family presented in this case study.

Patient	*50M*	*85M*	*80F*	*45F*	*13F*
Relationship to 50 M					
Health History					
COVID Test					
Fever					
Cough					
Dyspnea					
GI Symptoms					
Sore Throat					
Pneumonia					
Ventilation					
O_2 Supplementation					

21. Why did a middle-aged healthy adult (50M) have a severe infection and succumb to COVID-19?
22. Why did patient 50M, who was admitted with a viral infection, end up with infections such as bacterial and fungal infections?
23. Why do patients with severe infection, such as 50M and 85M, exhibit lymphopenia?
24. The doctors told 50M's wife that it is harder to treat fungal infections than it is to treat bacterial infections. Why is this so?
25. Why was the helmet non-invasive positive-pressure ventilation (NIPPV) used in 50M and why was he sedated?
26. Compare the two laboratory parameters of 50M from May 6 and May 18 (Table 5), and identify the ones that have changed abnormally. What is the cause for, and the consequence of, these changes?
27. What is convalescent plasma therapy and what is the eligibility to receive this treatment?
28. List two major organ systems that help maintain pH balance and briefly explain how they achieve this.
29. Why did 50M experience pH and electrolyte fluctuations as his condition worsened? What does this indicate?
30. How is dialysis normally performed and what are the challenges faced by the doctor in performing this procedure, particularly in patients such as 50M?

Questions for Further Research

Use the following questions to continue to research appropriate sources to stay abreast of the emerging field of COVID-19 research.

1. What are the current treatment plans for an individual with COVID-19 who has a) mild, b) moderate or c) severe infection? Are they readily accessible to people of different socio-economic status around the globe?
2. There are many researchers and companies that have successfully introduced vaccines that work effectively with minimal side effects. Name a few vaccines that are in the forefront and describe how they work. If you choose to get vaccinated, or already have, which of these would you opt to receive and why?
3. The vaccines target the spike protein on the membrane of the virus. Which part(s) of the virus is/are also being targeted in the process of producing other therapeutics? Will this be a preferable choice of treatment for anti-vaxxers?
4. Similar to SARS-CoV-2, SARS-CoV (the virus that resulted in the epidemic in 2003) used spike protein to bind to ACE2 receptors. Based on your reading and knowledge, why is SARS-CoV-2 infection more virulent and severe than SARS-CoV?
5. Would Patient 50M have a different outcome had he been tested and treated promptly on his first visit to the primary care physician?

Advanced Questions in Pathophysiology

1. Identify the common causes of a stomach ulcer and explain the pathophysiology behind it.
2. Explain how *Salmonella* infection causes inflammation and diarrhea.
3. Explain why an infection causes tachycardia.
4. Explain the pathophysiology of the onset of pneumonia in COVID patients. Why does this cause a drop in oxygen saturation?